PROPOSED PROFESSIONAL INFORMATION FOR

BORTEZOMIB 3.5 MG EUROLAB

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

BORTEZOMIB 3.5 MG EUROLAB (Powder for solution for injection)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each BORTEZOMIB 3.5 MG EUROLAB vial contains 3,5 mg bortezomib (as a mannitol boronic ester).

After reconstitution for intravenous administration, 1 mL of solution contains 1 mg bortezomib.

For subcutaneous administration 1 mL of the reconstituted solution contains 2,5 mg bortezomib.

The product contains mannitol.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for solution for injection.

White to off-white freeze-dried cake or powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

BORTEZOMIB 3.5 MG EUROLAB for injection is indicated for:

Multiple Myeloma

- as monotherapy or in combination with pegylated liposomal doxorubicin or dexamethasone for the treatment of adult patients with progressive multiple myeloma who have received at least 1 prior therapy and who have already undergone or are unsuitable for haematopoietic stem cell transplantation;
- in combination with dexamethasone, or with dexamethasone and thalidomide, for the induction treatment of adult patients with previously untreated multiple myeloma who are eligible for high dose chemotherapy with haematopoietic stem cell transplantation;
- in combination with melphalan and prednisone for the treatment of adult patients with previously untreated multiple myeloma who are not eligible for high-dose chemotherapy with haematopoietic stem cell transplantation.

Mantle Cell Lymphoma

- treatment of relapsed or refractory mantle cell lymphoma for patients who have received at least one prior line of therapy, one of which should have included an anthracycline (or mitoxantrone) and/ or rituximab as part of their chemotherapy regime.
- treatment for newly diagnosed mantle cell lymphoma (MCL) in adults, in combination with rituximab, cyclophosphamide, doxorubicin and prednisone who are unsuitable for haematopoietic stem cell transplantation.

4.2 Posology and method of administration

Posology

BORTEZOMIB 3.5 MG EUROLAB must be administered by a medical practitioner experienced in the treatment of cancer.

BORTEZOMIB 3.5 MG EUROLAB lyophilised powder for solution for injection is available for:

- intravenous administration at a concentration of 1 mg/mL (as a 3 to 5 second bolus injection) or
- subcutaneous administration at a concentration of 2,5 mg/mL.

Because each route of administration has a different reconstituted concentration, caution should be used when calculating the volume to be administered.

BORTEZOMIB 3.5 MG EUROLAB IS FOR INTRAVENOUS AND SUBCUTANEOUS USE ONLY and should not be given by other routes. Intrathecal administration has resulted in death.

See section 6.6 for Reconstitution Instructions.

BORTEZOMIB 3.5 MG EUROLAB retreatment may be considered for multiple myeloma patients who had previously responded to treatment with BORTEZOMIB 3.5 MG EUROLAB (see below).

Monotherapy

Relapsed Multiple Myeloma and Relapsed Mantle Cell Lymphoma

Recommended dosage

- The recommended starting dose of BORTEZOMIB 3.5 MG EUROLAB is 1,3 mg/m^2 body surface area (BSA) twice weekly for two weeks (on days 1, 4, 8, and 11), followed by a 10-day rest period (days 12 to 21).
- This 3-week period is considered a treatment cycle.
- At least 72 hours should elapse between consecutive doses of BORTEZOMIB 3.5 MG EUROLAB.
- It is recommended that patients with a confirmed complete response receive 2 additional cycles of BORTEZOMIB 3.5 MG EUROLAB beyond a confirmation.

- It is also recommended that responding patients who do not achieve a complete remission receive a total of 8 cycles of BORTEZOMIB 3.5 MG EUROLAB therapy.

Recommended dosage adjustments during treatment and re-initiation of treatment

BORTEZOMIB 3.5 MG EUROLAB treatment must be withheld at the onset of any

- Grade 3 non-haematological, or any
- Grade 4 haematological toxicities, excluding neuropathy as discussed below (see also section 4.4).
- Once the symptoms of the toxicity have resolved, BORTEZOMIB 3.5 MG EUROLAB treatment may be re-initiated at a 25 % reduced dose (1,3 mg/m^2 reduced to 1,0 mg/m^2 or 1,0 mg/m^2 reduced to 0,7 mg/m^2).

If the toxicity is not resolved or if it recurs at the lowest dose, discontinuation of BORTEZOMIB 3.5 MG EUROLAB must be considered unless the benefit of treatment clearly outweighs the risk.

Patients who experience BORTEZOMIB 3.5 MG EUROLAB related neuropathic pain and/or peripheral neuropathy are to be managed as presented in Table 1 below.
Severe autonomic neuropathy resulting in treatment interruption or discontinuation has been reported. Patients with pre-existing severe neuropathy may be treated with BORTEZOMIB 3.5 MG EUROLAB only after careful risk/benefit assessment.

Table 1: Recommended dose modifications for BORTEZOMIB 3.5 MG EUROLAB related neuropathic pain and/or peripheral sensory neuropathy or motor neuropathy.

Severity of peripheral neuropathy Signs and Symptoms [a]	**Modification of dose and regimen**
Grade 1 (asymptomatic; paraesthesia,	No action.

weakness and/or loss of deep tendon reflexes) with no pain or loss of function	
Grade 1 with pain or Grade 2 (moderate symptoms; limiting Instrumental Activities of daily living (ADL))[b]	Reduce BORTEZOMIB 3.5 MG EUROLAB to 1,0 mg/m^2 OR Change BORTEZOMIB 3.5 MG EUROLAB treatment schedule to 1,3 mg/m^2 once per week
Grade 2 with pain or Grade 3 (severe symptoms; limiting self-care ADL[c])	Withhold BORTEZOMIB 3.5 MG EUROLAB treatment until symptoms of toxicity have resolved. When toxicity resolves re-initiate BORTEZOMIB 3.5 MG EUROLAB treatment and reduce dose to 0,7 mg/m^2 and change treatment schedule to once per week.
Grade 4 (life threatening consequences; urgent intervention indicated)	Discontinue BORTEZOMIB 3.5 MG EUROLAB

[a] Grading based on NCI Common Toxicity Criteria CTCAE v 4.0

[b] *Instrumental ADL*: refers to preparing meals, shopping for groceries or clothes, using telephone, managing money or other such daily activities.

[c] *Self-care ADL*: refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden

Combination therapy

Previously Untreated Multiple Myeloma – Patients who are Not Eligible for Stem Cell Transplantation

Recommended dosage in combination with Melphalan and Prednisone

BORTEZOMIB 3.5 MG EUROLAB for injection is administered in combination with oral melphalan and oral prednisone for nine 6-week treatment cycles as shown in Table 2.

- In cycles 1 to 4, BORTEZOMIB 3.5 MG EUROLAB is administered twice weekly (on days 1, 4, 8, 11, 22, 25, 29 and 32).
- In cycles 5 to 9, BORTEZOMIB 3.5 MG EUROLAB is administered once weekly (on days 1, 8, 22 and 29).

Table 2: Recommended dosage regimen for BORTEZOMIB 3.5 MG EUROLAB when used in combination with melphalan and prednisone for patients with previously untreated multiple myeloma who are not eligible for stem cell transplantation.

Twice weekly BORTEZOMIB 3.5 MG EUROLAB (Cycles 1-4)												
Week	**1**				**2**		**3**	**4**		**5**		**6**
B (1,3 mg/m^2)	Day 1	-	-	Day 4	Day 8	Day 11	rest period	Day 22	Day 25	Day 29	Day 32	rest period
M (9 mg/m^2) P (60 mg/m^2)	Day 1	Day 2	Day 3	Day 4	-	-	rest period	-	-	-	-	rest period

Once weekly (cycles 5-9)									
Week	1				2	3	4	5	6
B (1,3 mg/m^2)	Day 1	-	-	-	Day 8	rest period	Day 22	Day 29	rest period
M (9 mg/m^2) P (60 mg/m^2)	Day 1	Day 2	Day 3	Day 4	-	rest period	-	-	rest period

[B]= BORTEZOMIB 3.5 MG EUROLAB M=Melphalan P= Prednisone

Dose management guidelines for combination therapy with Melphalan and Prednisone.

Dose modification and re-initiation of therapy when BORTEZOMIB 3.5 MG EUROLAB is administered in combination with melphalan and prednisone.

Prior to initiating a new cycle of therapy:

- Platelet count should be ≥ 70 x 10^9/L. and absolute neutrophil count (ANC) should be ≥ 1,0 x 10^9/L.
- Non-haematological toxicities should have resolved to Grade 1 or baseline (See Table 3 below).

Table 3: Dose modifications during subsequent cycles:

Toxicity	**Dose modification or delay**
Haematological toxicity during a cycle:	
• If prolonged Grade 4 neutropenia or thrombocytopenia, or thrombocytopenia with bleeding is observed in the previous cycle	Consider reduction of the melphalan dose by 25 % in the next cycle.
• If platelet count is ≤ 30 x 10^9/ ℓ or ANC is ≤ 0,75 x 10^9/ ℓ on a BORTEZOMIB 3.5 MG EUROLAB dosing day (other than Day 1)	BORTEZOMIB 3.5 MG EUROLAB dose should be withheld.
If several BORTEZOMIB 3.5 MG EUROLAB doses in a cycle are withheld (≥ 3 doses during twice weekly administration or ≥ 2 doses during weekly administration)	BORTEZOMIB 3.5 MG EUROLAB dose should be reduced by 1 dose level (from 1,3 mg/m^2 to 1 mg/m^2, or from 1,0 mg/m^2 to 0,7 mg/m^2)
Grade ≥ 3 non-haematological toxicities	BORTEZOMIB 3.5 MG EUROLAB therapy should be withheld until symptoms of the

	toxicity have resolved to Grade 1 or baseline. Then, BORTEZOMIB 3.5 MG EUROLAB may be reinitiated with one dose level reduction (from 1,3 mg/m^2 to 1 mg/m^2, or from 1,0 mg/m^2 to 0,7 mg/m^2). For BORTEZOMIB 3.5 MG EUROLAB-related neuropathic pain and/or peripheral neuropathy, hold and/or modify BORTEZOMIB 3.5 MG EUROLAB dose as outlined in Table 1.

For additional information concerning melphalan and prednisone, refer to the respective professional information leaflets.

Previously Untreated Multiple Myeloma – Patients who are Eligible for Stem Cell Transplantation

Recommended Dosage

The recommended starting dose of BORTEZOMIB 3.5 MG EUROLAB in combination with other medicines used for the treatment of multiple myeloma is 1,3 mg/m^2 to be administered twice weekly on Days 1, 4, 8, and 11, followed by a rest period of 10-18 days, which is considered a treatment cycle. Three to 6 cycles should be administered. At least 72 hours should elapse between consecutive doses of BORTEZOMIB 3.5 MG EUROLAB.

For BORTEZOMIB 3.5 MG EUROLAB dosage adjustments for transplant eligible patients follow dose modification guidelines described under monotherapy (Table 1) above.

For dosing instructions for other medicines combined with BORTEZOMIB 3.5 MG EUROLAB, see their respective professional information leaflets.

Relapsed Multiple Myeloma

Recommended Dosage in Combination with Pegylated Liposomal Doxorubicin for BORTEZOMIB 3.5 MG EUROLAB dosage and dose modifications, see Monotherapy.

Pegylated liposomal doxorubicin is administered at 30 mg/m^2 on day 4 of the BORTEZOMIB 3.5 MG EUROLAB 3-week regimen as a 1-hour intravenous infusion administered after the BORTEZOMIB 3.5 MG EUROLAB injection.
For additional information concerning pegylated liposomal doxorubicin, see respective professional information leaflet.

Recommended Dosage in Combination with Dexamethasone

For BORTEZOMIB 3.5 MG EUROLAB dosage and dose modifications, see Monotherapy.

Dexamethasone is administered orally at 20 mg on the day of, and the day after, BORTEZOMIB 3.5 MG EUROLAB administration.

For additional information concerning dexamethasone, see respective professional information leaflet.

Retreatment for Multiple Myeloma

Patients who have previously responded to treatment with BORTEZOMIB 3.5 MG EUROLAB (either alone or in combination) and who have relapsed should be started on retreatment at the last tolerated dose. Refer to Monotherapy for dosing schedule.

Previously Untreated Mantle Cell Lymphoma

Recommended Dosage in Combination with Rituximab, Cyclophosphamide, Doxorubicin and Prednisone

For BORTEZOMIB 3.5 MG EUROLAB dosage, see Monotherapy. Six BORTEZOMIB 3.5 MG EUROLAB cycles are administered.

For patients with a response first documented at Cycle 6, two additional BORTEZOMIB 3.5 MG EUROLAB cycles are recommended.

The following medicines are administered on Day 1 of each BORTEZOMIB 3.5 MG EUROLAB 3-week treatment cycle as intravenous infusions: rituximab at 375 mg/m^2, cyclophosphamide at 750 mg/m^2, and doxorubicin at 50 mg/m^2. Prednisone is administered orally at 100 mg/m^2 on Days 1, 2, 3, 4 and 5 of each treatment cycle.

Dose Adjustments during Treatment for Patients with Previously Untreated Mantle Cell Lymphoma

Prior to the first day of each cycle (other than Cycle 1):

- Platelet count should be ≥ 100 x 10^9/L and absolute neutrophil count (ANC) should be ≥ 1,5 x 10^9/L
- Haemoglobin should be ≥ 8 g/dL (≥ 4,96 mmol/L)
- Non-haematologic toxicity should have recovered to Grade 1 or baseline

BORTEZOMIB 3.5 MG EUROLAB treatment must be withheld at the onset of any Grade 3 non- haematological or Grade 3 haematological toxicities, excluding neuropathy (see also section 4.4). For dose adjustments, see Table 4 below.

Granulocyte colony stimulating factors may be administered for haematologic toxicity according to local standard practice. Prophylactic use of granulocyte colony stimulating factors should be considered in case of repeated delays in cycle administration. Platelet

transfusion for the treatment of thrombocytopenia should be considered when clinically appropriate.

Table 4: Dose Adjustments during Treatment for Patients with Previously Untreated Mantle Cell Lymphoma

Toxicity	**Posology modification or delay**
Haematological toxicity • ≥Grade 3 neutropenia with fever, Grade 4 neutropenia lasting more than 7 days, a platelet count < 10 x10^9/L	BORTEZOMIB 3.5 MG EUROLAB therapy should be withheld for up to 2 weeks until the patient has an ANC ≥ 0,75 x 10^9/L and a platelet count ≥ 25 x 10^9/L. • If, after BORTEZOMIB 3.5 MG EUROLAB has been held, the toxicity does not resolve, as defined above, then BORTEZOMIB 3.5 MG EUROLAB must be discontinued. • If toxicity resolves i.e., patient has an ANC ≥ 0,75 x 10^9/L and a platelet count ≥ 25 x 10^9/L, BORTEZOMIB 3.5 MG EUROLAB dose should be reduced by 1 dose level (from 1,3 mg/m^2 to 1 mg/m^2, or from 1 mg/m^2 to 0,7 mg/m^2).
• If platelet counts < 25 x10^9/L. or ANC < 0,75 x 10^9/L on a BORTEZOMIB 3.5 MG EUROLAB dosing day (other than Day 1)	BORTEZOMIB 3.5 MG EUROLAB dose should be withheld

Grade ≥ 3 non-haematological toxicities	BORTEZOMIB 3.5 MG EUROLAB therapy should be withheld until symptoms of the toxicity have resolved to Grade 2 or better. Then, BORTEZOMIB 3.5 MG EUROLAB may be reinitiated with one dose level reduction (from 1,3 mg/m^2 to 1 mg/m^2, or from 1 mg/m^2 to 0,7 mg/m^2). For BORTEZOMIB 3.5 MG EUROLAB-related neuropathic pain and/or peripheral neuropathy, hold and/or modify BORTEZOMIB 3.5 MG EUROLAB as outlined in Table 1.

For dosing instructions for rituximab, cyclophosphamide, doxorubicin, or prednisone, see the respective professional information leaflet.

Special populations

Paediatric patients

BORTEZOMIB 3.5 MG EUROLAB has not been studied in children and adolescents. Therefore, it should not be used in the paediatric age group until further data become available.

Elderly patients

There is no evidence to suggest that dose adjustments are necessary in the elderly (see section 4.8).

Patients with renal impairment

The pharmacokinetics of BORTEZOMIB 3.5 MG EUROLAB are not influenced by the degree of renal impairment. Therefore, dosing adjustments of BORTEZOMIB 3.5 MG EUROLAB are not necessary for patients with renal insufficiency. Since dialysis may reduce BORTEZOMIB 3.5 MG EUROLAB concentrations, BORTEZOMIB 3.5 MG EUROLAB should be administered after the dialysis procedure (see section 5.2).

Patients with hepatic impairment

Patients with mild hepatic impairment do not require a starting dose adjustment and should be treated per the recommended BORTEZOMIB 3.5 MG EUROLAB dose. Patients with moderate to severe hepatic impairment should be started on BORTEZOMIB 3.5 MG EUROLAB at a reduced dose of 0,7 mg/m^2 per injection during the first cycle, and a subsequent dose escalation to 1,0 mg/m^2 or further dose reduction to 0,5 mg/m^2 may be considered based on patient tolerance (see Table ~~2~~5 below).

Table 5: Recommended starting dose modification for BORTEZOMIB 3.5 MG EUROLAB in patients with hepatic impairment.

Grade of hepatic impairment*	**Bilirubin level**	**SGOT (AST) levels**	**Modification of starting dose**
Mild	≤ 1,0 x ULN	> ULN	None
	> 1,0 x -1,5 x ULN	Any	None
Moderate	> 1,5 x -3 x ULN	Any	Reduce BORTEZOMIB 3.5 MG EUROLAB to 0,7 mg/m^2 in the first cycle. Consider dose escalation to 1,0 mg/m^2 or further dose reduction to 0,5 mg/m^2 in subsequent cycles based on patient tolerability.
Severe	> 3x ULN	Any	

Abbreviations: SGOT= serum glutamic oxaloacetic transaminase;

AST= aspartate aminotransferase, ULN= upper limit of the normal range.

*Based on NCI Organ Dysfunction Working Group classification for categorising hepatic impairment (mild, moderate, severe).

Method of Administration

Administration Precautions

There have been fatal cases if inadvertent intrathecal administration of bortezomib, as in BORTEZOMIB 3.5 MG EUROLAB.

DO NOT ADMINISTER BORTEZOMIB 3.5 MG EUROLAB INTRATHECALLY.

Intravenous Injection:

The reconstituted solution is administered as a 3 - 5 second bolus intravenous injection through a peripheral or central intravenous catheter followed by a flush with 0,9 % sodium chloride solution for injection.

At least 72 hours should elapse between consecutive doses of BORTEZOMIB 3.5 MG EUROLAB.

Subcutaneous Injection:

The reconstituted solution is injected into the thighs (right or left) or abdomen (right or left). Injection sites should be rotated for successive injections.

If local site reactions occur following BORTEZOMIB 3.5 MG EUROLAB injection subcutaneously, a less concentrated BORTEZOMIB 3.5 MG EUROLAB solution (1 mg/mL instead of 2,5 mg/mL) may be administered subcutaneously or changed to IV injection.

4.3 Contraindications

- Hypersensitivity to bortezomib or to any of the excipients listed in section 6.1.
- Acute diffuse infiltrative pulmonary and pericardial disease.
- When BORTEZOMIB 3.5 MG EUROLAB is given in combination with other medicines, refer to their Professional Information (PI) for additional contraindications.

4.4 Special warnings and precautions for use

When BORTEZOMIB 3.5 MG EUROLAB is given in combination with other medicines, Professional Information's of these other medicines must be consulted prior to initiation of treatment with BORTEZOMIB 3.5 MG EUROLAB.

Intrathecal administration

There have been fatal cases of inadvertent intrathecal administration of bortezomib, as in BORTEZOMIB 3.5 MG EUROLAB. BORTEZOMIB 3.5 MG EUROLAB 3,5 mg powder for solution for injection is for intravenous or subcutaneous use. BORTEZOMIB 3.5 MG EUROLAB should not be administered intrathecally.

DO NOT ADMINISTER BORTEZOMIB 3.5 MG EUROLAB INTRATHECALLY.

Gastrointestinal toxicity

Gastrointestinal toxicity, including nausea, diarrhoea, vomiting and constipation are very common with bortezomib treatment. Reactions usually occur early in treatment (Cycles 1 and 2) and may persist for several cycles. Patients experiencing treatment emergent gastrointestinal toxicity may benefit from administration of anti-emetics and anti-diarrhoeals. Fluid and electrolyte replacement should be administered to prevent or treat dehydration. Cases of ileus have been uncommonly reported (see section 4.8). Therefore, patients who experience constipation should be closely monitored.

Haematological toxicity

Bortezomib treatment is very commonly associated with haematological toxicities (thrombocytopenia, neutropenia and anaemia).
Gastrointestinal and intracerebral haemorrhage have been reported in association with bortezomib treatment. However, febrile neutropenia is an uncommon undesirable effect. The most common haematologic toxicity is transient thrombocytopenia, which generally resolves between treatment cycles. In clinical studies it was reported that platelets were lowest at Day 11 of each cycle of bortezomib treatment and typically recovered to baseline by the next cycle. The cyclical pattern of platelet count decrease, and recovery remain consistent in studies of multiple myeloma and mantle cell lymphoma, with no evidence of cumulative thrombocytopenia or neutropenia in any of the regimens studied.

Therefore, platelet counts should be monitored prior to each dose of BORTEZOMIB 3.5 MG EUROLAB. BORTEZOMIB 3.5 MG EUROLAB therapy should be withheld when the platelet count is < 25,000/µL or, in the case of combination with melphalan and prednisone, when the platelet count is ≤ 30,000/µL (see section 4.2 and 4.8). Severe bleeding, including central nervous system (CNS) and gastrointestinal bleeding, associated with thrombocytopenia, has been reported.

Potential benefit of the treatment should be carefully weighed against the risks, particularly in case of moderate to severe thrombocytopenia and risk factors for bleeding.
Complete blood counts (CBC) with differential and including platelet counts should be frequently monitored throughout treatment with BORTEZOMIB 3.5 MG EUROLAB. Platelet transfusion, red blood cell (RBC) transfusions and administration of growth factors may be utilised in the management of haematological toxicities. Prophylactic platelet transfusions should be considered in thrombocytopenic patients at high risk of bleeding.

In patients with MCL, transient neutropenia that was reversible between cycles was observed, with no evidence of cumulative neutropenia. Since patients with neutropenia are at increased risk of infections, they should be monitored for signs and symptoms of infection and treated promptly. Granulocyte colony stimulating factors may be administered for haematologic toxicity according to local standard practice. Prophylactic use of granulocyte colony stimulating factors should be considered in case of repeated delays in cycle administration (see section 4.2).

In a multiple myeloma study of bortezomib vs dexamethasone, the mean platelet count reported was approximately 40 % of baseline. The incidence of significant bleeding events (≥ Grade 3) was similar on both the bortezomib (4 %) and dexamethasone (5 %) arms.

In a combination study of bortezomib with rituximab, cyclophosphamide, doxorubicin and prednisone in previously untreated mantle cell lymphoma patients, the incidence of thrombocytopenia adverse events (≥ Grade 4) was reported as 32 % bortezomib with rituximab, cyclophosphamide, doxorubicin and prednisone versus 2 % for the rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone arm. The incidence of bleeding adverse events (≥ Grade 3) was 1,7 % (4 patients) in the bortezomib with rituximab, cyclophosphamide, doxorubicin and prednisone arm and was 1,2 % (3 patients) in the rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone arm.

There were no deaths due to bleeding events reported in either arm. There were no CNS bleeding events in the bortezomib with rituximab, cyclophosphamide, doxorubicin and prednisone arm; there was 1 bleeding event in the rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone arm. Platelet transfusions were given to 23 % of the patients in the bortezomib with rituximab, cyclophosphamide, doxorubicin and prednisone arm and 3 % of the patients in the rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone arm.

The incidence of neutropenia (≥ Grade 4) was 70 % in the bortezomib with rituximab, cyclophosphamide, doxorubicin and prednisone arm and 52 % in the rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone arm. The incidence of febrile neutropenia (≥ Grade 4) was 5 % in the bortezomib with rituximab, cyclophosphamide, doxorubicin and prednisone arm and 6 % in the rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone arm. Colony-stimulating factor support was provided at a rate of 78 % in the bortezomib with rituximab, cyclophosphamide, doxorubicin and prednisone arm and 61 % in the rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone arm.

Herpes zoster virus reactivation

Antiviral prophylaxis is recommended in patients being treated with BORTEZOMIB 3.5 MG EUROLAB.

In studies in patients with previously untreated multiple myeloma, the overall incidence of herpes zoster reactivation was very common in patients treated with bortezomib, melphalan and prednisone.

Hepatitis B Virus (HBV) reactivation and infection

When rituximab is used in combination with BORTEZOMIB 3.5 MG EUROLAB, HBV screening must always be performed in patients at risk of infection with HBV before initiation of treatment. Carriers of hepatitis B and patients with a history of hepatitis B must be closely monitored for clinical and laboratory signs of active HBV infection during and following rituximab combination treatment with BORTEZOMIB 3.5 MG EUROLAB. Antiviral prophylaxis should be considered. Refer to the Summary of Product Characteristics of rituximab for more information.

Progressive multifocal leukoencephalopathy (PML)

Very rare cases with unknown causality of John Cunningham (JC) virus infection, resulting in PML and death, have been reported in patients treated with bortezomib. Patients diagnosed with PML had prior or concurrent immunosuppressive therapy. Most cases of PML were diagnosed within 12 months of their first dose of bortezomib. Patients should be monitored at regular intervals for any new or worsening neurological symptoms or signs that may be suggestive of PML as part of the differential diagnosis of CNS problems. If a diagnosis of PML is suspected, patients should be referred to a specialist in PML and appropriate diagnostic measures for PML should be initiated. Discontinue BORTEZOMIB 3.5 MG EUROLAB if PML is diagnosed.

Peripheral neuropathy

Treatment with bortezomib is very commonly associated with peripheral neuropathy, which is predominantly sensory. However, cases of severe motor neuropathy with or without sensory peripheral neuropathy have been reported. Patients with pre-existing symptoms (numbness, pain or a burning feeling in the feet or hands) and/or signs of peripheral neuropathy are likely to experience worsening peripheral neuropathy (including ≥ Grade 3) during treatment with bortezomib. The incidence of peripheral neuropathy increases early in the treatment and has been observed to peak during cycle 5.

It is recommended that patients be carefully monitored for symptoms of neuropathy such as a burning sensation, hyperesthesia, hypoesthesia, paraesthesia, discomfort, neuropathic pain or weakness. Patients with pre-existing peripheral neuropathy or at high risk of peripheral neuropathy may benefit from starting BORTEZOMIB 3.5 MG EUROLAB subcutaneously.

Patients experiencing new or worsening peripheral neuropathy should undergo neurological evaluation and may require a change in the dose, schedule or route of administration to subcutaneous (see section 4.2). Neuropathy has been managed with supportive care and other therapies. Peripheral neuropathy may not be reversible.

Early and regular monitoring for symptoms of treatment-emergent neuropathy with neurological evaluation should be considered in patients receiving BORTEZOMIB 3.5 MG EUROLAB in combination with medicines known to be associated with neuropathy (e.g. thalidomide) and appropriate dose reduction or treatment discontinuation should be considered.

In addition to peripheral neuropathy, there may be a contribution of autonomic neuropathy to some adverse reactions such as postural hypotension and severe constipation with ileus. Information on autonomic neuropathy and its contribution to these undesirable effects is limited.

Seizures

Seizures have been uncommonly reported in patients without previous history of seizures or epilepsy. Special care is required when treating patients with any risk factors for seizures.

Hypotension

Bortezomib treatment is commonly associated with orthostatic/postural hypotension. Most adverse reactions are mild to moderate in nature and are observed throughout treatment. Patients who developed orthostatic hypotension on bortezomib (injected intravenously) did not have evidence of orthostatic hypotension prior to treatment with bortezomib. Most patients required treatment for their orthostatic hypotension. A minority of patients with orthostatic hypotension experienced syncopal events. Orthostatic/postural hypotension was not acutely related to bolus infusion of bortezomib. The mechanism of this event is unknown although a component may be due to autonomic neuropathy. Autonomic neuropathy may be related to bortezomib or bortezomib may aggravate an underlying condition such as diabetic or amyloidotic neuropathy. Caution is advised when treating patients with a history of syncope receiving medicines known to be associated with hypotension; or who are dehydrated due to recurrent diarrhoea or vomiting. Management of orthostatic/postural hypotension may include adjustment of antihypertensive medicines, rehydration or

administration of mineralocorticosteroids and/or sympathomimetics. Patients should be instructed to seek medical advice if they experience symptoms of dizziness, light-headedness or fainting spells.

Posterior Reversible Encephalopathy Syndrome (PRES)

There have been reports of PRES in patients receiving bortezomib. PRES is a rare, often reversible, rapidly evolving neurological condition, which can present with seizure, hypertension, headache, lethargy, confusion, blindness, and other visual and neurological disturbances. Brain imaging, preferably Magnetic Resonance Imaging (MRI), is used to confirm the diagnosis. In patients developing PRES, BORTEZOMIB 3.5 MG EUROLAB should be discontinued. The safety of reinitiating bortezomib therapy in patients previously experiencing PRES is not known.

Heart failure

Acute development or exacerbation of congestive heart failure, and/or new onset of decreased left ventricular ejection fraction has been reported during bortezomib treatment. Fluid retention may be a predisposing factor for signs and symptoms of heart failure. Patients with risk factors for or existing heart disease should be closely monitored. Patients using angiotensin converting enzyme inhibitors, beta-blockers, antihypertensives, calcium channel blockers, angiotensin receptor blockers and diuretics may have a higher incidence of cardiac failure during bortezomib treatment.

Electrocardiogram investigations

There have been isolated cases of QT-interval prolongation in studies, causality has not been established.

Pulmonary disorders

There have been rare reports of acute diffuse infiltrative pulmonary disease of unknown aetiology such as pneumonitis, interstitial pneumonia, lung infiltration, and acute respiratory distress syndrome (ARDS) in patients receiving bortezomib (see section 4.8). Some of these events have been fatal. A pre-treatment chest radiograph is recommended to serve as a baseline for potential post-treatment pulmonary changes.
In the event of new or worsening pulmonary symptoms (e.g., cough, dyspnoea), a prompt diagnostic evaluation should be performed, and patients treated appropriately.
Specific regimen with concomitant administration with high-dose cytarabine (2 g/m^2 per day) by continuous infusion over 24 hours is not recommended.

Renal impairment

Renal complications are frequent in patients with multiple myeloma. Patients with renal impairment should be monitored closely (see sections 4.2 and 5.2).

Hepatic impairment

Bortezomib is metabolised by liver enzymes. Bortezomib exposure is increased in patients with moderate or severe hepatic impairment; these patients should be treated with BORTEZOMIB 3.5 MG EUROLAB at reduced doses and closely monitored for toxicities (see sections 4.2 and 5.2).

Hepatic reactions

Rare cases of hepatic failure have been reported in patients receiving bortezomib and concomitant medicines and with serious underlying medical conditions. Other reported hepatic reactions include increases in liver enzymes, hyperbilirubinaemia, and hepatitis. Such changes may be reversible upon discontinuation of bortezomib (see section 4.8).

Tumour lysis syndrome

Because bortezomib is a cytotoxic medicine and can rapidly kill malignant plasma cells and MCL cells, the complications of tumour lysis syndrome may occur. The patients at risk of tumour lysis syndrome are those with high tumour burden prior to treatment. These patients should be monitored closely, and appropriate precautions taken. Symptoms of tumour lysis syndrome are weakness, vomiting, cramps, seizure, oedema and fluid overload, congestive heart failure, dysrhythmias and syncope.

Concomitant medicines

Patients should be closely monitored when given bortezomib in combination with potent CYP3A4-inhibitors. Caution should be exercised when bortezomib is combined with CYP3A4- or CYP2C19 substrates (see section 4.5).

Normal liver function should be confirmed, and caution should be exercised in patients receiving oral hypoglycaemics (see section 4.5).

Potentially immunocomplex-mediated reactions

Potentially immunocomplex-mediated reactions, such as serum-sickness-type reaction, polyarthritis with rash and proliferative glomerulonephritis have been reported uncommonly. BORTEZOMIB 3.5 MG EUROLAB should be discontinued if serious reactions occur.

Amyloidosis

The impact of proteasome inhibition by bortezomib on disorders associated with protein accumulation such as amyloidosis is unknown. Caution is advised in these patients.

4.5 Interactions with other medicines and other forms of interaction

In vitro studies indicate that bortezomib is a weak inhibitor of the cytochrome P450 (CYP) isozymes 1A2, 2C9, 2C19, 2D6 and 3A4. Based on the limited contribution of CYP2D6 to the metabolism of bortezomib, the CYP2D6 poor metaboliser phenotype is not expected to affect the overall disposition of bortezomib.

Patients should be closely monitored when given bortezomib in combination with potent CYP3A4 inhibitors (e.g. ketoconazole, ritonavir).

There was no significant effect on the pharmacokinetics of bortezomib, when an assessment was done on the effect of omeprazole, a potent CYP2C19 inhibitor, on the pharmacokinetics of bortezomib (injected intravenously).

Concomitant use of bortezomib with strong CYP3A4 inducers (e.g., rifampicin, carbamazepine, phenytoin, phenobarbital and St. John's Wort) is not recommended, as efficacy may be reduced.

There was no significant effect on the pharmacokinetics of bortezomib, when the effect of dexamethasone, a weaker CYP3A4 inducer, was assessed on the pharmacokinetics of bortezomib (injected intravenously).

The effect of melphalan-prednisone on the pharmacokinetics of bortezomib (injected intravenously), is not considered clinically relevant.

Patients on oral antidiabetic medicines receiving BORTEZOMIB 3.5 MG EUROLAB treatment may require close monitoring of their blood glucose levels and adjustment of the dose of their antidiabetic medicines. During clinical trials, hypoglycaemia and hyperglycaemia were reported in diabetic patients receiving oral hypoglycaemics.

Patients should be cautioned about the use of concomitant medications that may be associated with peripheral neuropathy (such as amiodarone, anti-virals, isoniazid, nitrofurantoin, or statins), or with a decrease in blood pressure.

4.6 Fertility, pregnancy and lactation

Contraception in males and females

Male patients treated with BORTEZOMIB 3.5 MG EUROLAB should be advised to use highly effective contraception, until the end of relevant systemic exposure to the genotoxic compound including potential genotoxic metabolites (i.e. five half-lives (2 months) after the

last dose) plus 90 days, (i.e 60-75 days for sperm production plus 10-14 days for the transport to epididymis).

Female patients and female sexual partners of male patients receiving BORTEZOMIB 3.5 MG EUROLAB should be advised to use highly effective contraception, until the end of relevant systemic exposure to the genotoxic compound including potential genotoxic metabolites (i.e. five half-lives (2 months) after the last dose) plus 6 months (which covers the growth and maturation phase of folliculogenesis).

Pregnancy

Safety in pregnancy has not been established. No clinical data are available for bortezomib with regard to exposure during pregnancy. The teratogenic potential of bortezomib has not been fully investigated.

If BORTEZOMIB 3.5 MG EUROLAB is used during pregnancy, alone or in combination with other medicines, or if the patient becomes pregnant while receiving this medicine, the patient should be informed of potential for hazard to the foetus.

Breast-feeding

Safety in lactation has not been established. It is not known whether bortezomib is excreted in human milk. Because of the potential for serious adverse reactions in breast-fed infants from mothers on BORTEZOMIB 3.5 MG EUROLAB, breast-feeding should be discontinued during treatment with BORTEZOMIB 3.5 MG EUROLAB.

Fertility

Fertility studies were not conducted with bortezomib.

4.7 Effects on ability to drive and use machines

BORTEZOMIB 3.5 MG EUROLAB may have a moderate influence on the ability to drive and use machines. BORTEZOMIB 3.5 MG EUROLAB is frequently associated with fatigue, dizziness, orthostatic/postural hypotension or blurred vision and less frequently syncope. Therefore, patients must be cautious when driving or using machines and should be advised not to drive or operate machinery if they experience these symptoms (see section 4.8).

4.8 Undesirable effects

a) Summary of the safety profile

Serious adverse reactions less frequently reported during treatment with bortezomib, as in BORTEZOMIB 3.5 MG EUROLAB include cardiac failure, tumour lysis syndrome, pulmonary hypertension, posterior reversible encephalopathy syndrome, acute diffuse infiltrative pulmonary disorders and rarely autonomic neuropathy.

The most frequently reported adverse reactions during treatment with bortezomib, as in BORTEZOMIB 3.5 MG EUROLAB are nausea, diarrhoea, constipation, vomiting, fatigue, pyrexia, thrombocytopenia, anaemia, neutropenia, peripheral neuropathy (including sensory), headache, paraesthesia, decreased appetite, dyspnoea, rash, herpes zoster and myalgia.

b) Tabulated summary of adverse reactions

System organ class	Frequent	Less frequent	Frequency unknown
Infections and infestations	Herpes zoster (including disseminated & ophthalmic), Pneumonia, Herpes simplex,	Infection, Bacterial infections, Viral infections, Sepsis (including septic shock), Bronchopneumonia, Herpes virus infection,	Meningoencephalitis herpetic

	Fungal infection	Bacteraemia (including staphylococcal), Hordeolum, Influenza, Cellulitis, Device related infection, Skin infection, Ear infection, Staphylococcal infection, Tooth infection, Meningitis (including bacterial), Epstein-Barr virus infection, Genital herpes, Tonsillitis, Mastoiditis, Post viral fatigue syndrome	
Neoplasms benign, malignant and unspecified (including cysts and polyps)		Neoplasm malignant, Leukaemia plasmacytic, Renal cell carcinoma, Mass, Mycosis fungoides, Neoplasm benign	
Blood and lymphatic system disorders	Thrombocytopenia, Neutropenia, Anaemia, Leukopenia, Lymphopenia	Pancytopenia, Febrile neutropenia, Coagulopathy, Leukocytosis, Lymphadenopathy, Disseminated intravascular coagulation, Thrombocytosis, Hyperviscosity syndrome, Platelet disorder NOS,	Haemolytic anaemia, Thrombotic microangiopathy (including thrombocytopenic purpura)

		Blood disorder NOS, Haemorrhagic diathesis, Lymphocytic infiltration	
Immune system disorders		Hypersensitivity, Anaphylactic shock, Amyloidosis, Type III immune complex mediated reaction	Angioedema
Endocrine disorders		Cushing's syndrome, Hyperthyroidism, Inappropriate antidiuretic hormone secretion, Hypothyroidism	
Metabolism and nutrition disorders	Decreased appetite, Dehydration, Hypokalaemia, Hyponatraemia, Blood glucose abnormal, Hypocalcaemia, Enzyme abnormality	Tumour lysis syndrome, Failure to thrive, Hypomagnesaemia, Hypophosphataemia, Hyperkalaemia, Hypercalcaemia, Hypernatraemia, Uric acid abnormal, Diabetes mellitus, Fluid retention, Hypermagnesaemia, Acidosis, Electrolyte imbalance, Fluid overload, Hypochloraemia, Hypovolaemia,	

		Hyperchloraemia, Hyperphosphataemia, Metabolic disorder, Vitamin B complex deficiency, Vitamin B12 deficiency, Gout, Increased appetite, Alcohol intolerance	
Psychiatric disorders	Mood disorders and disturbances, Anxiety disorder, Sleep disorders and disturbances	Mental disorder, Hallucination, Psychotic disorder, Confusion, Restlessness, Suicidal ideation, Adjustment disorder, Delirium, Libido decreased	
Nervous system disorders	Neuropathies, Peripheral sensory neuropathy, Dysaesthesia, Neuralgia, Motor neuropathy, Loss of consciousness (including syncope), Dizziness, Dysgeusia, Lethargy, Headache	Tremor, Peripheral sensorimotor neuropathy, Dyskinesia, Cerebellar coordination and balance disturbances, Memory loss (excluding dementia), Encephalopathy, Neurotoxicity, Seizure disorders, Post herpetic neuralgia, Speech disorder, Restless legs syndrome, Migraine, Sciatica, Disturbance in attention, Reflexes	Posterior Reversible Encephalopathy Syndrome, Guillain-Barré syndrome, Demyelinating polyneuropathy

		abnormal, Parosmia, Cerebral haemorrhage, Haemorrhage intracranial (including subarachnoid), Brain oedema, Transient ischaemic attack, Coma, Autonomic nervous system imbalance, Autonomic neuropathy, Cranial palsy, Paralysis, Paresis, Presyncope, Brain stem syndrome, Cerebrovascular disorder, Nerve root lesion, Psychomotor hyperactivity, Spinal cord compression, Cognitive disorder NOS, Motor dysfunction, Nervous system disorder NOS, Radiculitis, Drooling, Hypotonia	
Eye disorders	Eye swelling, Vision abnormal, Conjunctivitis	Eye haemorrhage, Eyelid infection, Eye inflammation, Diplopia, Dry eye, Eye irritation, Eye pain, Lacrimation increased, Eye discharge, Corneal lesion, Exophthalmos,	Chalazion, Blepharitis, Optic neuropathy

		Retinitis, Scotoma, Eye disorder (inc. eyelid) NOS, Dacryoadenitis acquired, Photophobia, Photopsia, Different degrees of visual impairment (up to blindness)	
Ear and labyrinth disorders	Vertigo	Dysacusis (including tinnitus), Hearing impaired (up to and including deafness), Ear discomfort, Ear haemorrhage, Vestibular neuronitis, Ear disorder NOS	
Cardiac disorders		Cardio-pulmonary arrest, Cardiac fibrillation (including atrial), Cardiac failure (including left and right ventricular), Dysrhythmia, Tachycardia, Palpitations, Angina pectoris, Pericarditis (including pericardial effusion), Cardiomyopathy, Ventricular dysfunction, Bradycardia, Atrial flutter, Myocardial infarction,	Cardiac tamponade

		Atrioventricular block, Cardiovascular disorder (including cardiogenic shock), Torsade de pointes, Angina unstable, Cardiac valve disorders, Coronary artery insufficiency, Sinus arrest	
Vascular disorders	Hypotension, Orthostatic hypotension, Hypertension	Deep vein thrombosis, Haemorrhage, Thrombophlebitis (including superficial), Circulatory collapse (including hypovolaemic shock), Phlebitis, Flushing, Haematoma (including perirenal), Poor peripheral circulation, Vasculitis, Hyperaemia (including ocular), Peripheral embolism, Lymphoedema, Pallor, Erythromelalgia, Vasodilatation, Vein discolouration, Venous insufficiency	Cerebrovascular accident
Respiratory system, thoracic and mediastinal disorders	Dyspnoea, Epistaxis, Upper/lower respiratory tract infection, Cough	Pulmonary embolism, Pleural effusion, Pulmonary oedema (including acute),	Pulmonary alveolar haemorrhage

		Bronchospasm, Chronic obstructive pulmonary disease, Hypoxaemia, Respiratory tract congestion, Hypoxia, Pleurisy, Hiccups, Rhinorrhoea, Dysphonia, Wheezing, Respiratory failure, Acute respiratory distress syndrome, Apnoea, Pneumothorax, Atelectasis, Pulmonary hypertension, Haemoptysis, Hyperventilation, Orthopnoea, Pneumonitis, Respiratory alkalosis, Tachypnoea, Pulmonary fibrosis, Bronchial disorder, Hypocapnia, Interstitial lung disease, Lung infiltration, Throat tightness, Dry throat, Increased upper airway secretion, Throat irritation, Upper airway cough syndrome	
Gastrointestinal disorders	Nausea and vomiting symptoms,	Pancreatitis (including chronic), Haematemesis,	Colitis ischaemic

	Diarrhoea, Constipation, Gastrointestinal haemorrhage (including mucosal), Dyspepsia, Stomatitis, Abdominal distension, Oropharyngeal pain, Abdominal pain (including gastrointestinal and splenic pain), Oral disorder, Flatulence	Lip swelling, Gastrointestinal obstruction (including small intestinal obstruction, ileus), Abdominal discomfort, Oral ulceration, Enteritis, Gastritis, Gingival bleeding, Gastroesophageal reflux disease, Colitis (including clostridium difficile), Gastrointestinal inflammation, Dysphagia, Irritable bowel syndrome, Gastrointestinal disorder NOS, Tongue coated, Gastrointestinal motility disorder, Salivary gland disorder, Pancreatitis acute, Peritonitis, Tongue oedema, Ascites, Oesophagitis, Cheilitis, Faecal incontinence, Anal sphincter atony, Faecaloma, Gastrointestinal ulceration and perforation, Gingival hypertrophy, Megacolon,	

		Rectal discharge, Oropharyngeal blistering, Lip pain, Periodontitis, Anal fissure, Change of bowel habit, Proctalgia, Abnormal faeces	
Hepatobiliary disorders	Hepatic enzyme abnormality	Hepatotoxicity (including liver disorder), Hepatitis, Cholestasis, Hepatic failure, Hepatomegaly, Budd-Chiari syndrome, Cytomegalovirus hepatitis, Hepatic haemorrhage, Cholelithiasis	
Skin and subcutaneous tissue disorders	Rash, Pruritus, Erythema, Dry skin	Erythema multiforme, Urticaria, Acute febrile neutrophilic dermatosis, Toxic skin eruption, Dermatitis, Hair disorder, Petechiae, Ecchymosis, Skin lesion, Purpura, Skin mass, Psoriasis, Hyperhidrosis, Night sweats, Acne, Blister, Pigmentation disorder, Skin reaction, Jessner's lymphocytic infiltration, Palmarplantar	Toxic epidermal necrolysis, Stevens-Johnson syndrome, Decubitus ulcer

		erythrodysaesthesia syndrome, Haemorrhage subcutaneous, Livedo reticularis, Skin induration, Papule, Photosensitivity reaction, Seborrhoea, Cold sweat, Skin disorder NOS, Erythrosis, Skin ulcer, Nail disorder	
Musculoskeletal and connective tissue disorders	Musculoskeletal pain, Muscle spasms, Pain in extremity, Muscular weakness	Muscle twitching, Joint swelling, Arthritis, Joint stiffness, Myopathies, Sensation of heaviness, Rhabdomyolysis, Temporomandibular joint syndrome, Fistula, Joint effusion, Pain in jaw, Bone disorder, Musculoskeletal and connective tissue infections and inflammations, Synovial cyst	
Renal and urinary disorders	Renal impairment	Renal failure acute, Renal failure chronic, Urinary tract infection, Urinary tract signs and symptoms, Haematuria, Urinary retention,	

		Micturition disorder, Proteinuria, Azotaemia, Oliguria, Pollakiuria, Bladder irritation	
Reproductive system and breast disorders		Vaginal haemorrhage, Genital pain, Erectile dysfunction, Testicular disorder, Prostatitis, Breast disorder female, Epididymal tenderness, Epididymitis, Pelvic pain, Vulval ulceration	
Congenital, familial and genetic disorders		Aplasia, Gastrointestinal malformation, Ichthyosis	
General disorders and administration site conditions	Pyrexia, Fatigue, Asthenia, Oedema (including peripheral), Chills, Pain, Malaise(2O.4)	General physical health deterioration, Face oedema, Injection site reaction, Mucosal disorder, Chest pain, Gait disturbance, Feeling cold, Extravasation, Catheter related complication, Change in thirst, Chest discomfort, Feeling of body temperature change, Injection site pain, Death (including sudden), Multi-organ failure, Injection site	

		haemorrhage, Hernia (including hiatus), Impaired healing, Inflammation, Injection site phlebitis, Tenderness, Ulcer, Irritability, Non-cardiac chest pain, Catheter site pain, Sensation of foreign body	
Investigations	Weight decreased	Hyperbilirubinaemia, Protein analyses abnormal, Weight increased, Blood test abnormal, C-reactive protein increased, Blood gases abnormal, Electrocardiogram abnormalities (inc QT prolongation), International normalised ratio abnormal, Gastric pH decreased, Platelet aggregation increased, Troponin I increased, Virus identification and serology, Urine analysis abnormal	
Injury, poisoning and procedural		Fall, Contusion, Transfusion reaction,	

complications		Fractures, Rigors, Face injury, Joint injury, Burns, Laceration, Procedural pain, Radiation injuries	
Surgical and medical procedures		Macrophage activation	

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website or to Eurolab (Pty) Ltd. by email: drug-safety@eurolab.co.za. By reporting side effects, you can help provide more information on the safety of BORTEZOMIB 3.5 MG EUROLAB.

4.9 Overdose

In patients, overdose more than twice the recommended dose has been associated with the acute onset of symptomatic hypotension and thrombocytopenia with fatal outcomes.
There is no known specific antidote for bortezomib overdose. In the event of an overdose, the patient's vital signs should be monitored and appropriate supportive care given to maintain blood pressure (such as fluids, pressors, and/or inotropic agents) and body temperature (see sections 4.2 and 4.4). Hypotension should be treated aggressively with intravenous hydration and other clinically appropriate measures.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 26 Cytostatic agents

Pharmacotherapeutic group: Antineoplastic agents, other antineoplastic agents, ATC code: L01XG01.

Mechanism of action

Bortezomib is a selective proteasome inhibitor. Il specifically inhibits the chymotrypsin-like activity of the 26S proteasome in mammalian cells.

Bortezomib mediated proteasome inhibition affects cells in a number of ways, including, but not limited to, altering regulatory proteins, which control cell cycle progression and Nuclear Factor kappa B (NF-kB) activation. Inhibition of the proteasome results in cell cycle arrest and apoptosis. NF-kB is a transcription factor whose activation is required for many aspects of tumourogenesis, including cell growth and survival, angiogenesis, cell:cell interactions, and metastasis. In myeloma, bortezomib affects the ability of myeloma cells to interact with the bone marrow microenvironment.
Experiments have demonstrated that bortezomib is cytotoxic to a variety of cancer cell types and that cancer cells are more sensitive to the proapoptotic effects of proteasome inhibition than normal cells. Bortezomib causes reduction of tumour growth *in vivo* in many preclinical tumour models, including multiple myeloma.

5.2 Pharmacokinetic properties

Absorption

Following intravenous bolus administration of a 1,0 mg/m^2 and 1,3 mg/m^2 dose to patients with multiple myeloma, the mean maximum plasma concentrations of bortezomib are 57 and 112 mg/mL respectively after the first dose. In subsequent doses, mean maximum observed plasma concentrations range from 67 to 106 ng/mL tor the 1,0 mg/m^2 dose and 89 to 120 ng/mL for the 1,3 mg/m^2 dose.

Distribution

The mean distribution volume of bortezomib is variable and ranges from 1659 litres to 3294 litres following single- or repeat-dose administration of 1,0 mg/m^2 or 1,3 mg/m^2 to patients with multiple myeloma. This suggests that bortezomib distributes widely to peripheral tissues. The binding of bortezomib to human plasma average 83 % over the concentration range 100 - 1000 mg/mL.

Biotransfromation

In vitro studies with human liver microsomes and human cDNA-expressed cytochrome P450 isozymes indicate that bortezomib is primarily oxidatively metabolised via cytochrome P450 enzymes, 3A4, 2C19, and 1A2. Bortezomib metabolism by CYP 2D6 and 2C9 enzymes is minor. The major metabolic pathway is deboronation to form two deboronated metabolites that subsequently undergo hydroxylation to several metabolites. Deboronated-bortezomib metabolites are inactive as 26S proteasome inhibitors. Plasma data at 10 min and 30 min after dosing indicate that the plasma levels of metabolites are low compared to the parent.

Elimination

The mean elimination half-life of bortezomib upon multiple dosing range from 40-193 hours. Bortezomib is eliminated more rapidly following the first dose compared to subsequent doses. Mean total body clearances are 102 and 112 L/h following the first dose for doses of 1,0 mg/m^2 and 1,3 mg/m^2, respectively, and range from 15 to 32 L/h and 18 to 32 L/h following subsequent doses for doses of 1,0 mg/m^2 and 1,3 mg/m^2, respectively.

Special populations:

Age, Gender and Race

Based on a population pharmacokinetic analysis, clearance of bortezomib increase with increasing body surface area (BSA). After correcting for the BSA effect, other demographics such as age, body weight and sex did not have clinically significant effects on bortezomib clearance. BSA-normalised clearance of bortezomib in paediatric patients are similar to that

observed in adults.

The effects of gender and race on the pharmacokinetics of bortezomib have not been evaluated.

Hepatic Impairment

The effect of hepatic impairment (see Table 5 for hepatic impairment classification) on the pharmacokinetics of bortezomib was assessed at bortezomib doses ranging from 0,5 to 1,3 mg/m^2. Mild hepatic impairment does not alter dose- normalised bortezomib AUC. However. the dose-normalised mean AUC values are increased by approximately 60 % in patients with moderate or severe hepatic impairment. A lower starting dose is recommended in patients with moderate or severe hepatic impairment, and those patients should be monitored closely (see Table 5).

Renal Impairment

A pharmacokinetic study conducted in patients with various degrees of renal impairment who were classified according to their creatinine clearance values (CrCL) into the following groups: Normal (CrCL ≥ 60 mL min/1,73 m^2), Mild (CrCL =40-59 mL/min/1,73 m^2), Moderate (CrCL =20-39 mL/min/1,73 m^2) and Severe (CrCL < 20 mL/min/1,73 m^2). A group of dialysis patients who were dosed after dialysis was also included in the study. Patients were administered intravenous doses of 0,7 to 1,3 mg/m^2 of bortezomib twice weekly. Exposure of bortezomib (dose-normalised AUC and C_{max}) was comparable among all the groups (see section 4.2).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

The inactive ingredients include mannitol and nitrogen.

6.2 Incompatibilities

This medicine must not be mixed with other products, except those mentioned in section 6.6.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at or below 30 °C.

Keep in the outer carton in order to protect from light, until required for use.

KEEP OUT OF REACH OF CHILDREN.

Reconstituted solution:

When reconstituted under aseptic conditions, BORTEZOMIB 3.5 MG EUROLAB is stable for 24 hours at 25 °C (stored in the original vial and/or syringe).

From a microbiological point of view, unless the method of opening/reconstitution precludes the risk of microbial contamination, BORTEZOMIB 3.5 MG EUROLAB should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

6.5 Nature and contents of container

BORTEZOMIB 3.5 MG EUROLAB is packed in 10 mL Type I clear glass vials, closed with grey bromobutyl rubber stoppers and grey aluminium caps, fitted with red plastic flip-off disc.

6.6 Special precautions for disposal and other handling

General precautions

Bortezomib is a cytotoxic agent. Therefore, caution should be used during handling and preparation of BORTEZOMIB 3.5 MG EUROLAB. Use of gloves and other protective clothing to prevent skin contact is recommended.

Aseptic technique must be strictly observed throughout the handling of BORTEZOMIB 3.5 MG EUROLAB, since it contains no preservative.

There have been fatal cases of inadvertent intrathecal administration of bortezomib.

BORTEZOMIB 3.5 MG EUROLAB 3,5 mg powder for solution for injection is for intravenous or subcutaneous use. BORTEZOMIB 3.5 MG EUROLAB should not be administered intrathecally.

Instructions for reconstitution

BORTEZOMIB 3.5 MG EUROLAB must be reconstituted by a healthcare professional.

Intravenous injection

Each 10 mL vial of BORTEZOMIB 3.5 MG EUROLAB must be carefully reconstituted with 3,5 mL of sodium chloride 9 mg/mL (0,9 %) solution for injection, by using a syringe of the appropriate size, without removing the vial stopper. Dissolution of the lyophilised powder is completed in less than 2 minutes.

After reconstitution, each 1 mL solution contains 1 mg bortezomib. The reconstituted solution is clear and colourless, with a final pH of 4 to 7.

The reconstituted solution must be inspected visually for particulate matter and discolouration prior to administration. If any discolouration or particulate matter is observed, the reconstituted solution must be discarded.

Subcutaneous injection

Each 10 mL vial of BORTEZOMIB 3.5 MG EUROLAB must be carefully reconstituted with 1,4 mL of sodium chloride 9 mg/mL (0,9 %) solution for injection, by using a syringe of the appropriate size, without removing the vial stopper. Dissolution of the lyophilised powder is completed in less than 2 minutes.

After reconstitution, each mL solution contains 2,5 mg bortezomib. The reconstituted solution is clear and colourless, with a final pH of 4 to 7. The reconstituted solution must be inspected

visually for particulate matter and discolouration prior to administration. If any discolouration or particulate matter is observed, the reconstituted solution must be discarded.

Disposal

BORTEZOMIB 3.5 MG EUROLAB is for single use only. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Eurolab (Pty) Ltd.

Woodmead Office Park,

3 Stirrup Lane, Van Reenens Avenue,

Woodmead,

2144

8 REGISTRATION NUMBERS

56/26/0620

9 DATE OF FIRST AUTHORISATION

17 September 2024

10 DATE OF REVISION OF TEXT

Not applicable

11 DOSIMETRY

Not applicable

12 INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS

Not applicable